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(54) Title: COMPOSITION CONTAINING ANTIHISTAMINE H_2 RECEPTOR ANTAGONISTS AND BIOADHESIVE MATERIAL

(57) Abstract

Buffered pharmaceutical compositions for the local treatment of gastric disorders comprising a histamine H_2-receptor antagonist in intimate admixture with a bioadhesive material.

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Composition containing antihistamine H2 receptor antagonists and bioadhesive material.

This invention relates to the treatment of gastric disorders and pharmaceutical compositions for use therein. More particularly the invention relates to the local treatment of gastric disorders, especially acute gastric disorders such as acid indigestion, heartburn and gastritis, and gastric and peptic ulcer, using orally administrable pharmaceutical compositions comprising a histamine H_2-receptor antagonist contained within a drug delivery system. Compositions for use in the invention are specifically adapted to provide local delivery across the stomach wall to the H_2-receptor on the parietal cell receptor.

Histamine H_2-receptor antagonists, for example cimetidine, ranitidine, nizetidine and famotidine, reduce acid secretion by acting directly on the acid-secreting parietal cell located within the gastric gland of the stomach wall.

Although histamine H_2-receptor antagonists are remarkably effective in the treatment of many gastric disorders, in particular peptic and gastric ulcers, there exist certain patient groups which do not respond to treatment. In addition, the time lapse between dosing and onset of action, limits the potential benefit of histamine H_2-receptor antagonists in the treatment of acute, self-limiting gastric disorders.

A significant proportion of gastric and peptic ulcer patients, referred to as non-responders, do not respond to conventional histamine H_2-receptor antagonist therapy. (Walker et al.: Frequent non-response to histamine H_2-receptor antagonists in cirrhotics; Gut, 30, 1105-9, 1989; and Brack A. et al.: Clinical failures with cimetidine; Surgery, 88(3), 417-24.

In addition, the known poor respons to histamine H_2-receptor antagonist treatment by hypersecreting patients, for example critically ill, multiple trauma patients (Martin L. et al.: Failure of cimetidine prophylaxis in the critically ill; Arch. Surg., 114, 492-6, 1979) or those with Zollinger-Ellison syndrome (Stabile B.G. et al.: Failure of histamine H_2-receptor antagonist therapy in Zollinger-Ellison syndrome; Am. J. Surg., 145, 17-23, 1983) has led to the development of alternative treatments, notably the use of proton-pump inhibitors.

Histamine H_2-receptor antagonists are of potential benefit in the self-medication of acute, self-limiting gastric disorders such as hyperacidity. However, their slow onset of action is unlikely to meet the consumer requirement for rapid relief of symptoms.

Moreover, it will be appreciated that use of high dose levels in an attempt to achieve rapid relief of symptoms is not appropriate for non-prescription use. Indeed, a reduction from the standard therapeutic dose would be desirable for self-medication.

Co-administration of histamine H_2-receptor antagonists and other pharmaceutically active materials, including sucralfate and other antacids, has been investigated. The rationale for co-administration with antacid is that the antacid brings about rapid relief from the symptoms of excess stomach acidity by neutralisation whereas the histamine H_2-receptor antagonist acts independently by inhibiting secretion of acid from the parietal cell.

However, it is well known (Bodemar G. et al., Lancet, 1, 444-445, 1979; Mihaly G.W. et al., B.M.J., 285, 998-9, 1982; Lin. J.H. et al., B.J. Clin. Pharmacol. 24, 551-3, 1987)

that when histamine H_2-receptor antagonists are co-administered with antacids, especially antacids with high acid-neutralising capacity, a substantial reduction in the plasma bioavailability of the histamine H_2-receptor antagonist is frequently observed. Histamine H_2-receptor antagonist - antacid combinations are therefore generally contraindicated.

Bioadhesive materials have received considerable attention as platforms for controlled drug delivery. They can be targetted to specific drug administration sites, prolong the residence time and ensure an optimal contact with the absorbing surface. Many different types of bioadhesive materials, both natural and synthetic, can be used in the design of controlled drug delivery systems.

Sucralfate is a basic aluminium sulphate sucrose complex having ulcer healing and buffering properties. According to the literature, sucralfate has been shown to act by forming a bioadhesive gel structure which is believed to provide a local protective barrier. It has been reported that sucralfate does not interfere with the absorption of histamine H_2-receptor antagonists. Clinical studies have indicated a combination therapy to be of potential benefit.

EP-A-0 286 781 (Heumann Pharma) relates to pharmaceutical preparations with cytoprotective effect on the gastrointestinal tract containing a combination of a histamine H_2-receptor antagonist and an antacid substance which is able to give functional cytoprotection. Sucralfate is identified as an example of the antacid substance. It is described as giving functional cytoprotection but having a comparatively low acid-netutralising effect.

EP-A-0 403 048 (Warner-Lambert), published on December 19, 1990, describes medicated compositions comprising sucralfate and a therapeutically effective amount of a medicament which is a) substantially water insoluble, or b) a mixture of a water-soluble medicament and a release-delaying material which on admixture forms a substantially water-insoluble medicament. In a preferred embodiment, the medicament is selected from the group consisting of inter alia antacids and anti-ulcer medicaments. Compositions comprising sucralfate plus antacid and sucralfate plus an anti-ulcer medicament are described as cytoprotective compositions, useful in the treatment of peptic ulcers by forming an ulcer-adherent protective gel barrier.

EP-A-0 193 400 (Reckitt and Colman) describes pharmaceutical compositions comprising mixtures of a histamine H_2-receptor antagonist and sodium polyacrylate in the weight ratio 10 : 1 to 1 : 10. The compositions are described for use in the treatment of gastritis or of gastro-duodenal ulcers. The compositions may include an antacid. Use of antacid is described as resulting in a reduction in the viscosity of the liquid compositions, thereby providing some degree of viscosity control in the design of readily pourable liquid preparations.

US 4,615,697 (Robinson) discloses a controlled release composition comprising an effective amount of a treating agent, which may be a medicament, and a bioadhesive material which is a water-swellable and water-insoluble, fibrous, cross-linked carboxy-functional polymer. The controlled release compositions are described as adhering to the skin or to mucous membranes in the presence of water. Cimetidine is listed as an example of a medicament.

Current treatments using histamine H_2-receptor antagonists act systemically, i.e. the histamine H_2-receptor antagonist

is delivered to the parietal cell receptor from the blood.

International Patent Application No. PCT/GB91/00953 describes oral treatment of gastric disorders using a histamine H_2-receptor antagonist in combination with an antacid to promote local delivery of the histamine H_2-receptor antagonist to the receptor of the parietal cell wall. The increase in stomach wall receptor site bioavailability of the histamine H_2-receptor antagonist increases the capacity of the histamine H_2-receptor antagonist to reduce acid secretion compared with that of histamine H_2-receptor antagonist alone.

The increase in acid-secretion reducing capacity is described as being advantageous in the treatment of ulcer patients, in particular hypersecreting patients, in the treatment of those patients diagnosed as non-responders, and also to reduce the onset-phase of single-dose, self-medication for acute gastric disorders, for example gastric orders due to hyperacidity.

It has now been found that an intimate mixture comprising a histamine H_2-receptor antagonist with a bioadhesive material, for example sucralfate, buffered at or around the pKa of the histamine H_2-receptor antagonist, provides an effective therapy for gastric disorders, mediated through local delivery of the histamine H_2-receptor antagonist directly into the parietal cell receptor of the stomach wall.

Accordingly, the present invention provides the use of an orally administrable pharmaceutical composition comprising a histamine H_2-receptor antagonist and a bioadhesive material, for the manufacture of a medicament for the treatment of gastric disorders, characterised in that the composition is formulated as an intimate mixture whereby the bioadhesive

material and the histamine H_2-receptor antagonist form, in situ, a bioadhesive complex, locally targeting the histamine H_2-receptor antagonist to the stomach wall; and the composition is optimally buffered to confer a pH substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

The invention also provides a method of treatment of gastric disorders comprising administering to a sufferer an effective amount of a locally acting pharmaceutical composition comprising an intimate mixture of a histamine H_2-receptor antagonist and a bioadhesive material forming in situ a bioadhesive complex; and a buffering component to confer a pH substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

In a further aspect, the invention provides a locally acting pharmaceutical composition for use in the treatment of gastric disorders which comprises an intimate mixture of a histamine H_2-receptor antagonist and a bioadhesive material, and a buffering component to confer a pH substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

Bioadhesive materials for use in compositions of the present invention include materials, both natural and synthetic, which are capable of adhering to biological surfaces such as mucus membranes. Examples of bioadhesive materials include natural gums and plant extracts and synthetic materials such as sucralfate, cellulose derivatives, acrylic acid and methacrylic acid derivatives, for example cross-linked acrylic and methacrylic acid copolymers available under the Trade Names CARBOPOL and POLYCARBOPHIL.

Compositions for use in the invention are optimally buffered by the use of a buffering component which is suitably an antacid having equilibrium pH, acid neutralising capacity

and gastric residence time values which provide a pH profile with time conferring a local pH level substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

It will be appreciated that when the bioadhesive material is sucralfate which has buffering properties, it may function as the buffering component of the pharmaceutical composition.

This approach of locally delivering H_2-receptor antagonists via the stomach mucosa is of particular benefit in the self-medication of acute, self-limiting gastric disorders such as hyperacidity. It is understood that H_2-RA therapy fails in Zollinger-Ellison syndrome due to low levels of the drug at the H_2-receptor of the parietal cells. Local delivery according to the invention which increases the concentration of drug at the H_2-receptors of the parietal cell and renders the histamine H_2-receptor antagonist effective at low dosage levels, is regarded as of particular benefit in the treatment of these disorders.

Histamine H_2-receptor antagonists for use in compositions of the invention include cimetidine, ranitidine and famotidine, preferably cimetidine and ranitidine, and especially cimeditine. pKa values for known histamine H_2-receptor antagonists are readily available from pharmacological publications.

Similarly, the above-mentioned parameters for a suitable buffering component are readily available to those skilled in the art. Suitable buffering agents for use in compositions of the invention include aluminium hydroxide, magnesium hydroxide, aluminium hydroxide-magnesium carbonate co-dried gel, magnesium carbonate, magnesium oxide, magnesium aluminium silicate, magnesium trisilicate, sodium

bicarbonate, calcium carbonate, bismuth carbonate, alkali metal salts of citric, tartaric, benzoic, sorbic and phosphoric acid, and combinations thereof.

Further suitable antacids may be selected by pharmacokinetic analysis of the acid-secretion reducing capacity of a selected histamine H_2-receptor antagonist using a pharmacokinetic model based upon a modified, standard two-compartment model. With the introduction of further compartments to separately describe the stomach and the intestine, and with transport between the tissue compartment, representing the parietal cell tissue receptor compartment, and the stomach lumen, the model may be used to describe pharmacokinetics for a selected histamine H_2-receptor antagonist. The model demonstrates the reduction in local bioavailability of the histamine H_2-receptor antagonist at the parietal cell tissue receptor compartment as a function of gastric excretion and the increase in local bioavailability in the parietal cell tissue receptor compartment as a function of local, gastric absorption, and their dependence on gastric pH. Gastric pH levels are influenced by antacid. Thus, by inserting known values for equilibrium pH, acid neutralising capacity and gastric residence time, the suitability of any given antacid may be determined.

Conventional histamine H_2-receptor antagonist therapies act systemically and drug is distributed to all parts of the body via the bloodstream. Hence, it will be appreciated that non-target body tissues are exposed to drug. An advantage of a locally targeted drug delivery system is that low doses may be used and thus pharmacologically relevant doses are not achieved in non-target tissues.

Excretion of histamine H_2-r ceptor antagonist into the stomach lumen from the parietal cell tissue receptor causes a reduction in local bioavailability of the antagonist

whilst gastric absorption of histamine H_2-receptor antagonist into the parietal cell tissue receptor causes an increase in local bioavailability of the antagonist. An advantageous feature of the invention is the potential for using reduced dose levels of histamine H_2-receptor antagonist brought about by buffering the histamine H_2-receptor antagonist in the gastric environment, effectively reducing antagonist excretion into the stomach lumen, increasing absorption from the stomach lumen, and increasing the residence time of the histamine H_2-receptor antagonist in the gastric environment by forming a bioadhesive complex.

The dose level of histamine H_2-receptor antagonist may be selected according to the potency of the antagonist on a weight basis and according to the severity of the condition. For example where the histamine H_2-receptor antagonist is cimetidine or ranitidine it may be present in an amount from about 1 mg to 800 mg per dosage form, typically from about 5 mg to 50 mg for example 5, 10, 15, 20 or 25 mg.

It will be further appreciated that treatment with the present compositions provides a more rapid onset of action which renders them particularly suitable for the treatment of acute gastritis.

A further aspect of the invention is that the amount of antacid present in any given composition is independent of the dose of histamine H_2-receptor antagonist.

The bioadhesive material, for example sucralfate, may be present in an amount from about 100 mg to 1500 mg per dosage form, typically from about 800 mg to 1200 mg, for example 1000 mg.

These dosage levels encompass compositions where sucralfate serves as the buffering component and which do not include a further buffering agent.

Where a composition includes a bioadhesive material which has no buffering capacity or, in addition to sucralfate includes a further buffering agent, the level of buffer is optimally chosen to confer a pH substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

It is a feature of the buffering component that it serves a dual role. In one aspect, in the accepted mode of action of antacids, it brings about relief from the symptoms of excess stomach acidity by neutralisation. In a second aspect, and more importantly, it serves to act as an appropriate buffered vehicle to enhance the absorption of the histamine H_2-receptor antagonist. The dose of buffering agent may be selected to achieve both effects.

A suitable dose range for magnesium hydroxide is from about 150 mg to 3000 mg, for example from about 300 mg to 1500 mg, such as from about 300 mg to 600 mg.

A suitable dose range for aluminium hydroxide is from about 180 mg to 3600 mg, for example from about 360 mg to 1800 mg, such as from 360 to 720 mg.

A suitable dose range for sodium bicarbonate is from about 400mg to 8,000mg for example from about 800 mg to 4000mg, such as from about 800mg to 1600mg.

Compositions for use in the present invention may also contain pharmaceutically acceptable carriers. Compositions

may be formulated for oral administration in solid or liquid form, for example as tablets, capsules, powders, suspensions or dispersions. Compositions may thus be formulated by admixture with pharmaceutically acceptable vehicles additionally containing, as desired, pharmaceutically acceptable adjuvants including inter alia thickeners, preservatives, and colouring and flavouring agents.

It will be appreciated that certain pharmaceutical compositions for use in the present invention are novel and as such form a further aspect of the invention.

The following Examples illustrate the invention.

The examples include sucralfate as the bioadhesive material but are not limited thereto. Any material having bioadhesive properties, either a natural or synthetic material, may be incorporated into compositions for use in the invention.

Example 1

Entrapment of Cimetidine in Sucralfate

Cimetidine solutions were made up at pH 2.5 at concentrations in the range 0-200mg/ml. To 50ml of each cimetidine solution was added sucralfate (2g). 1 M HCl was added until a good paste was formed.

Results

mg/ml Cimetidine	Nature of Paste	Nature of supernatant
0	good	clear
50	good	clear
100	good	clear
125	good	clear
150	poor	cloudy suspension
200	no paste	cloudy suspension

The results show that concentrations of cimetidine below 150 mg/ml are most favourable for entrapment. At concentrations above 150 mg/ml paste integrity is affected.

Example 2

Cimetidine Entrapment and Release from Sucralfate

The level of entrapment of cimetidine in sucralfate and the release of the entrapped cimetidine into solutiion as a function of time was determined.

The levels of cimetidine studied were 0, 25, 50, 75, 100 and 125 mg/ml in a 50 ml volume.

Method

A preweighed amount of cimetidine was added to 0.1 M hydrochloric acid (30ml). The solution was mixed using a magnetic stirrer.

A pH probe was inserted into the solution and 1M hydrochloric acid was added until a clear solution (pH 2.5) was obtained. The volume was made up to 50ml. A 200 µl sample was removed.

Sucralfate (2g ex Katsura) was added with stirring and allowed to disperse. 1 M HCl was added in 200 µl aliquots until paste formation occurred. Stirring was continued until the supernatant was clear. A 200 µl sample of supernatant was removed.

The supernatant was poured off leaving the cimetidine/sucralfate paste.

0.1M HCl (50ml) was added, the mixture swirled for 10 seconds and a 200 µl sample removed. A further 50ml sample of 0.1 M HCl was added. A 200 µl sample was removed. A third 50ml sample of 0.1M HCl (pH 1.5) was added. The resulting mixture was placed on an orbital shaker (GFL.3017) at $^{3}/_{4}$ maximum speed.

200µl aliquots were removed after 1, 5, 15, 30 and 45 mins. and after 1, 1.5, 2, 2.5, 3, 3.5 and 4 hours.

At the end of the experiment 5M HCl (5ml) was added to dissolve the sucralfate. This final solution was diluted

and the total final level of sucralfate was determined.

Each of the 200µl samples removed throughout the experment was assayed as follows:

a 50µ sample was transferred to a vial and 1.95 ml. 0.1 M HCl was added. Further dilutions with distilled water were made as necessary. Optical density at 218mm was determined versus a distilled water blank.

Cimetidine Release (Corrected data)

Time Point (Mins)	Cimetidine concentrations (mg/ml)					
	0	25	50	75	100	125
01	0.0	0.05	0.06	0.187	0.507	0.680
05	0.0	0.086	0.166	0.249	0.609	0.945
15	0.0	0.138	0.314	0.549	0.966	1.734
30	0.0	0.193	0.519	0.738	1.364	2.120
45	0.0	0.237	0.645	0.948	1.691	2.488
60	0.0	0.274	0.743	1.107	1.942	2.828
90	0.0	0.323	0.855	1.43	2.337	3.494
120	0.0	0.363	0.935	1.665	2.675	3.868
150	0.0	0.382	1.039	1.969	2.865	4.220
180	0.0	0.406	1.13	2.176	3.203	4.448
210	0.0	0.438	1.162	2.285	3.419	4.596
240	0.0	0.439	1.185	3.012	3.438	4.497

Cimetidine Entrapment

Cimeditine (mg/ml)	Total Cimeditine added	Total Cimetidine in paste	% of total added entrapped
0	0.0	0.0	-
25	1175.5	59.35	5.05
50	2399.0	121.45	5.06
75	3497.0	166.0	4.75
100	4613.0	225.75	4.89
125	5207.5	263.75	5.06

At each cimetidine concentration, approximately 5% by weight of the available cimetidine is entrapped in sucralfate. Visual observations indicated that the integrity of the paste was interfered with at cimetidine concentrations in excess of 75mg/ml. Agitation caused pieces of the paste mass to break off.

The release data indicates that release from sucralfate is a diffusional process.

Example 3

The Effect of pH on Cimetidine release from Sucralfate Pastes

The rate of cimetidine release from sucralfate as a function of pH was determined at pH values 1.5, 3.0, 4.5, 6.0 and 7.5. The experiment was carried out using a cimetidine concentration of 50 mg/ml and 1g sucralfate.

	Theoretical pH Value				
	1.5	3.0	4.5	6.0	7.5
Total Cimetidine (mg):	1.079	1.082	1.117	1.105	1.045
Experimental pH: (initial)	1.69	3.23	4.64	6.12	7.54
Experimental pH: (5hrs)	3.21	3.17	4.57	6.18	7.66

The following table shows the release data as a function of % of total cimetidine entrapped within the sucralfate paste.

Time Points (Mins)	pH Value 1.5	3.0	4.5	6.0	7.5
01	6.95	6.65	5.28	9.41	6.32
05	12.6	19.50	14.50	11.31	6.96
15	21.87	31.89	23.63	15.48	11.20
30	32.16	37.15	27.48	19.91	15.98
45	42.08	42.79	29.45	25.16	21.44
60	51.62	44.82	32.86	28.69	26.69
90	68.39	50.09	39.21	34.93	35.89
120	83.5	57.02	41.99	40.0	45.26
150	94.16	61.28	46.46	47.87	54.74
180	104.54	65.25	48.97	52.04	63.83
210	111.21	68.69	52.28	56.29	72.63
240	119.55	70.06	54.43	60.27	81.24

The results show the greatest release of cimetidine from the paste exposed to the pH of 1.5. As the pH increases, th amount of cimetidine r leased decreases up to pH 4.5. Above this pH, the level of release increases again.

Example 4

Powder Formulations

The ingredients are dry blended under conditions of controlled temperature and humidity using conventional equipment.

Example 5 - 6

Tablet Formulations

The active antacid ingredients are granulated or spray dried in a conventional manner. The granule, the histamine H_2-receptor antagonist and the bioadhesive material are blended along with conventional tabletting aids, fillers and palatability aids and the blend is tabletted on a conventional machine.

Example 7

Liquid Suspensions

Aluminium hydroxide and magnesium hydroxide are received as commercially available suspensions. These active suspensions are added to a premix of thickeners. The resulting mixture is then blended with the histamine H_2-receptor antagonist, the bioadhesive material and preservatives and flavours as appropriate.

POWDER FORMULATIONS

Example 4

Formulation No.	1	2	3	4	5	6	7	8	9	10	11
Sucralfate	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Cimetidine	1-100	-	-	1-100	-	-	1-100	-	-	1-100	-
Ranitidine	-	1-100	-	-	1-100	-	-	1-100	-		1-100
Famotidine	-	-	1-20	-	-	1-20	-	-	1-20		-
Sodium Bicarbonate	1,500	1,750	2,000	750	875	1,500	1,500	1,750	2,000	-	-
Citric Acid	-	-	-	-	-	-	1,000	1,225	1,400	-	-
Tartaric Acid	-	-	-	-	-	-	600	70	800	-	-
Flavour	1	1	1	1	1	1	1	1	1	1	1
Icing Sugar	500	500	500	500	500	500	500	500	500	500	500

(all amounts in mg)

TABLET FORMULATIONS

Example 5

Fomulation No.	12	13	14	15	16	17	18	19	20	21	22
Sucralfate	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Cimetidine	1-100	-	-	1-100	-	-	1-100	-	-	1-100	-
Ranitidine	-	1-100	-	-	1-100	-	-	1-100	-		1-100
Famotidine	-	-	1-20	-	-	1-20	-	-	1-20		-
Aluminium Hydroxide	700	800	750	350	400	375	-	-	-	-	-
Magnesium Hydroxide	700	800	750	350	400	375	-	-	-	-	-
Calcium Carbonate	-	-	-	-	-	-	800	900	1,000	-	-
Starch	100	100	100	100	100	100	100	100	100	100	100
Icing Sugar	250	250	250	250	250	250	250	250	250	250	250
Flavour	2	2	2	2	2	2	2	2	2	2	2
Povidone	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	20	20	20	20	20	20	20	20	20	20	20

(all amounts in mg)

COMBINATION ANTACID TABLET FORMULATIONS

Example 6

Formulation No.	23	24	25	26	27	28	29	30	31
Sucralfate	1000	1000	1000	1000	1000	1000	1000	1000	1000
Cimetidine	1-100	-	-	1-100	-	-	1-100	-	-
Ranitidine	-	1-100	-	-	1-100	-	-	1-100	-
Famotidine	-	-	1-20	-	-	1-20	-	-	1-20
Sodium Bicarbonate	1000	1000	1000	2000	2000	2000			
Magnesium Aluminium Silicate	100	100	100	200	200	200	-	-	-
Hydro Calcite	125	125	125	250	250	250	250	250	250

(all amounts in mg)

Example 7

LIQUID SUSPENSIONS

Formulation No.	32	33	34
Sucralfate	1000	1000	1000
Cimetidine	1-100	-	-
Ranitidine	-	1-100	-
Famotidine	-	-	1-20
Magnesium Hydroxide	350	400	375
Aluminium Hydroxide	350	400	375
Sodium Bicarbonate	750	875	1,000
Sorbitol Solution	3,000	3,000	3,000
Preservatives	4.5	4.5	4.5
Flavour	10	10	10
Thickeners	45	45	45
Water	to volume		

(all amounts in mg)

Claims

1. The use of an orally administrable pharmaceutical composition comprising a histamine H_2-receptor antagonist and a bioadhesive material for the manufacture of a medicament for the treatment of gastric disorders, characterised in that the composition is formulated as an intimate mixture whereby the bioadhesive material and the histamine H_2-receptor antagonist form, in-situ, a bioadhesive complex, locally targeting the histamine H_2-receptor antagonist to the stomach wall; and the composition is optimally buffered to confer a pH substantially equal to that of the pKa of the histamine H_2-receptor antagonist, whereby local levels of the histamine H_2-receptor antagonist at the parietal cell receptor are increased.

2. Use as claimed in claim 1 characterised in that the composition is optimally buffered with a buffering component which is an antacid having equilibrium pH, acid neutralising capacity and gastric residence time values which provide a pH profile with time conferring a local pH level substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

3. Use as claimed in claim 1 or 2 for the treatment of gastric disorders in ulcer patients.

4. Use as claimed in claim 3 for the treatment of patients who do not respond to conventional histamine H_2-receptor antagonist therapy.

5. Use as claimed in claim 3 for the treatment of acid hypersecreting patients.

6. Use as claimed in claim 1 or 2 for the single-dose treatment of acute gastric disorders.

7. Use as claimed in any preceding claim whereby the histamine H_2-receptor antagonist is cimetidine, ranitidine, or famotidine.

8. Use as claimed in claim 7 whereby the histamine H_2-receptor antagonist is cimetidine.

9. Use as claimed in claim 8 whereby the dose level of cimetidine is from 1 to 800mg per dosage form.

10. Use as claimed in claim 9 whereby the dose level of cimetidine is from 5 to 50mg per dosage form.

11. Use as claimed in any preceding claim whereby the composition is buffered with aluminium hydroxide, magnesium hydroxide, aluminium hydroxide-magnesium carbonate co-dried gel, magnesium carbonate, magnesium oxide, magnesium trisilicate, sodium bicarbonate, calcium carbonate, bismuth carbonate, magnesium aluminium silicate, alkali metal salts of citric, tartaric, benzoic, sorbic or phosphoric acid, or combinations of any of the aforementioned antacids.

12. A method of treatment of gastric disorders comprising orally administering to a sufferer an effective amount of a pharmaceutical composition comprising an intimate mixture of a histamine H_2-receptor antagonist and a bioadhesive material, and a buffering component wherein the equilibrium pH, the acid neutralising capacity and the gastric residence time values confer a pH level substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

13. A pharmaceutical composition for use in the treatment of gastric disorders comprising an intimate mixture of a histamine H_2-receptor antagonist and a bioadhesive material, and a buffering component wherein the equilibrium pH, the acid neutralising capacity and the gastric residence time values confer a pH level substantially equal to that of the pKa of the histamine H_2-receptor antagonist.

INTERNATIONAL SEARCH REP RT

International Application No PCT/GB 91/02063

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/70. //(A 61 K 31/70 A 61 K 31:415)
(A 61 K 31/70 A 61 K 31:34) (A 61 K 31/70 A 61 K 31:425)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0403048 (WARNER-LAMBERT COMPANY) 19 December 1990, see page 7, lines 50-51; claims (cited in the application) ---	1-13
A	EP,A,0286781 (HEUMANN PHARMA GMBH & CO.) 19 October 1988, see claims (cited in the application) ---	1-13
A	EP,A,0381414 (E.R. SQUIBB & SONS, INC.) 8 August 1990, see claims ---	1-13
A	Chemical Abstracts, volume 103, no. 17, 1985 (Columbus, Ohio, US) S. Bank et al. "Prevention of duodenal ulcers in the rat using a combination of ranitidine and sucralfate in subtherapeutic doses", see page 66, abstract 134872q, & Gut, 1985, 26(6), 603-6 --- -/-	1-13

[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-03-1992	18. 03. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Maria Peis Maria Peis

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, volume 106, no. 9, 1987, (Columbus, Ohio, US) G. Mullersman et al.: "Lack of clinically significant in vitro and in vivo interactions between ranitidine and sucralfate", see page 19, abstract 60798h, & J. Pharm. Sci., 1986, 75(10), 995-8	1-13

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [x] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND INCOMPLETELY SEARCHABLE

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

In vieuw of the general wording of the terms "histamine H2-receptor antagonist" and "a bioadhesive material" as well as "buffering component", the search has been performed on the general idea and active agents mentionned in the examples. (E.P. art. 84, Guidelines, Part B, Chapt. II.7, last sentence and Chapt. III,3.7) Claims searched incompletely : 1-13

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9102063 SA 53494

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/03/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0403048	19-12-90	AU-A-	5703390	20-12-90
		CA-A-	2018945	14-12-90
		JP-A-	3024020	01-02-91
EP-A- 0286781	19-10-88	DE-A-	3710462	13-10-88
EP-A- 0381414	08-08-90	US-A-	4975281	04-12-90
		AU-A-	4859290	02-08-90
		CA-A-	2007334	30-07-90
		JP-A-	2270827	05-11-90